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Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia and challenges to clear it in patients with cardiac devices

Abstract

Infections related to cardiac implantable electronic devices present a significant challenge for specialists and often necessitate the removal of these devices. Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most common culprits behind these infections. When MRSA bacteremia occurs in conjunction with a cardiac device infection, imaging studies may not always confirm the involvement of the device. However, it is common practice to remove the entire device to effectively control the source of the infection. Patients may require long courses of antibiotic therapy, and sometimes a combination of two or more antibiotics is necessary to clear the associated bacteremia. Prophylactic treatment for presumptive endocarditis is frequently employed to prevent the infection from spreading to other parts of the body. Recurrence or persistence of MRSA bacteremia often mandates the removal of the cardiac device, raising concerns about the patient's reliance on the device. This manuscript aims to provide a comprehensive overview of the challenges in managing MRSA bacteremia in patients with cardiac devices, highlighting the complexities of diagnosis, treatment options, and the critical decisions surrounding device management.

Keywords: MRSA, implantable cardiac devices, bacteremia, biofilm, antibiotic therapy, infective endocarditis.

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Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) was described shortly after the introduction of methicillin in 1961; subsequently, several outbreaks of MRSA were reported in the early 1960s.[1,2] MRSA is defined as a *Staphylococcus aureus* with an oxacillin minimum inhibitory concentration (MIC) ≥4 mcg/mL. Isolates resistant to oxacillin or methicillin also are resistant to all beta-lactam agents, including cephalosporins.

Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a formidable clinical challenge, particularly in patients with cardiac devices. This paper offers a comprehensive review of the significant issues MRSA presents in producing bacteremia in these vulnerable populations. MRSA is a resilient pathogen, able to resist methicillin and other beta-lactam antibiotics, posing serious risks to patients with implanted cardiac devices such as pacemakers, implantable cardioverter-defibrillators (ICDs), and ventricular assist devices (VADs).[3]

One of the key challenges in treating MRSA infections is its ability to form biofilms on the surfaces of cardiac devices. These biofilms create a protective barrier, shielding the bacteria from antibiotics and the host's immune response, thus complicating treatment efforts.[4] This protective mechanism makes MRSA infections extremely hard to eradicate, often requiring a combination of diagnostic tools, such as blood cultures and advanced imaging techniques, to detect and monitor the infection's progression.

Further complicating the situation is MRSA's resistance to many standard antibiotics. In many cases, potent drugs like vancomycin or daptomycin are required; however, even these may not fully penetrate biofilms, making eradication of the infection difficult.[5] This often leaves healthcare professionals with a critical decision: should the infected device be surgically removed, or should the infection be managed with the device in place? Both approaches come with risks, as removing the device may carry significant surgical dangers; while retaining it could result in persistent infection.

The primary goal of this paper is to provide healthcare practitioners with a thorough understanding of MRSA-related bacteremia in patients with cardiac devices. It covers the epidemiology, pathogenesis, clinical presentation, diagnostic techniques, treatment options, and preventive strategies for managing this complex condition. By gaining insights into the challenges posed by MRSA, clinicians can enhance their ability to diagnose and treat these infections, ultimately improving patient outcomes.

Epidemiology

Bacteremia caused by MRSA is one of the leading causes of hospital-associated infections globally. Its prevalence varies significantly by country and region, depending on monitoring mechanisms and healthcare practices. The CDC estimates that MRSA annually causes over 70,000 severe infections and 9,000 deaths. Improvements in preventative measures such as contact precautions and hand hygiene have resulted in nearly 16% decrease in MRSA bacteremia, per the CDC's National Health Safety Network. A study from the Emerging Infections Program's (EIP) MRSA population surveillance from 2005 to2016 and from the Premier and Cerner Electronic Health Record databases from 2012 to 2017 found a similar decrease of 17.1% in hospital-acquired MRSA.[6,7]

Hospitalization and surgery are some of the leading risk factors for MRSA. Among these, patients who undergo procedures for cardiac device implantation are specifically at risk of developing bacteremia caused by MRSA due to the organism's ability to form biofilms on the device surface. A retrospective chart review of Beaumont Health System in Royal Oak, Michigan found that over a period of 10 years,

12,771 cardiac device implant, generator change, system revision procedures were performed with an infection rate of 1.2%. Out of the 218 patients with infection, MRSA was the causative agent in 44.9% of patients.[8]

It is estimated that approximately 225,000 pacemakers,[9] 114,000 implantable cardioverter-defibrillators (ICD)[10] and 57,000 cardiac resynchronization therapy (CRT)[11] are annually implanted in the United States. The amount of cardiac device implantation is expected to increase in the future with the increasing numbers the aging population and growing incidence cardiac disease.

Pathogenesis

The ability to up-regulate virulence factors under stressful stimuli (e.g., host immune response or circulating antibiotics) is a key factor in the enabling of *S. aureus* to persist in the bloodstream, to seed deep tissues, and to form secondary foci of infection. *S. aureus* strains have been effectively able to adhere to and colonize the skin and mucosa of nares, to invade the bloodstream, to evade host immunological responses, to form protective biofilms, and to develop resistance to several antibiotics. Consequently, despite the availability of many antibiotics with activity against wild-type strains, *S. aureus* is a highly successful and increasingly clinically important gram-positive pathogen.

***Adhesion and colonization*:** *S. aureus* can up-regulate a variety of virulence factors, enabling it to adhere to and colonize the nares and damaged skin or the surfaces of implanted devices or prostheses and to cause serious bloodstream infections. Teichoic acid, a polymer on the surface of *S. aureus*, is essential for this purpose.[12]

Invasion: *S. aureus* can disrupt the skin barrier by secreting exfoliate toxins,[13] hemolysins (including α-hemolysin [α-toxin], which forms pores in skin cell membranes), and various enzymes that destroy tissue.[14] Invasion may be triggered when the immune system is compromised, when there is a break in the physical integument, and/or when localized inflammation occurs.[15]

Evasion: *S. aureus* evades the host immune response by secreting anti-opsonizing proteins (e.g., chemotaxis inhibitory protein), which prevent phagocytosis by neutrophils.[16] Protein A, located on the surface of *S. aureus* cells, also has anti-phagocytic properties. Furthermore, *S. aureus* secretes leukotoxins (e.g., Panton-Valentine leukocidin), which lyse leukocytes, and expresses super antigens (e.g., enterotoxins and toxic shock syndrome toxin 1), which subvert the normal immune response by inducing strong, polyclonal stimulation and expansion of T cell receptor Vβ-specific T cells (followed by the deletion or suppression of these T cells to an anergic state).[17]

Biofilms: *S. aureus* quorum sensing may regulate gene expression to form slimy biofilms on damaged skin, fitted medical devices, and healthy or damaged heart valves. The depletion of nutrients and oxygen causes bacteria to enter a nongrowing state in which they are less susceptible to some antibiotics. In particular, small-colony variants of *S. aureus*, when adherent and in the stationary phase, demonstrate almost complete resistance to antimicrobial agents.[18] The biofilm matrix provides protection against immune cells and may restrict the penetration of some antibiotics.[19]

Antibiotic resistance: Strains of *S. aureus* have developed resistance to antibiotics, including penicillin, cephalosporins, methicillin, vancomycin, and linezolid. *S. aureus* abrogates the effects of penicillin by producing β-lactamase, and MRSA strains have acquired the *mec* gene, which encodes penicillin-binding protein 2a, and the *fem* gene, which confers resistance to methicillin, penicillinase-resistant penicillins, and cephalosporins.[20]

Clinical manifestation

Patients with cardiac devices may experience localized symptoms at the device site or systemic signs such as fever and septic shock when bacteremia caused by MRSA occurs. On physical examination redness, warmth, swelling, and tenderness may be observed at the site of the cardiac device implantation. Serious complications may arise, including endocarditis, sepsis, metastatic infections, chronic osteomyelitis, and device-associated endocarditis. Early identification of issues and the implementation of implementing aggressive treatment measures are imperative for improving patient outcomes.

Cardiac devices and types

Cardiac devices, such as medical implants or external devices, are essential in managing various heart conditions.[21] The primary categories of cardiac devices are the following:

Pacemaker: Cardiac pacemakers are effective treatments for various bradyarrhythmias. Despite the myriad of clinical situations in which permanent pacing is considered, most management decisions regarding permanent pacemaker implantation are driven by the following clinical factors:

- The association of symptoms with bradyarrhythmia
- The location of the conduction abnormality
- The absence of a reversible cause

Patients are often evaluated for permanent cardiac pacemaker placement due to symptoms that may be caused by bradyarrhythmias (e.g., dizziness, light-headedness, syncope, fatigue, and poor exercise tolerance). Cardiac pacemakers generally have two components that deliver the electrical impulse for myocardial stimulation: a pulse generator and electrodes (leads).[22]

Implantable cardioverter-defibrillators (ICDs): Implantable cardioverter-defibrillator (ICD) implantation is generally considered the first-line treatment option for the secondary prevention of sudden cardiac death (SCD) and for primary prevention in specific populations at high risk of SCD due to Ventricular tachycardia (VT) / Ventricular fibrillation (VF).

Cardiac resynchronization therapy (CRT) devices*:* Cardiac Resynchronization Therapy (CRT) devices are essential in treating heart failure patients with ventricular systolic dysfunction. CRT-P devices provide pacing to synchronize ventricular contractions, while CRT-D devices additionally provide defibrillation to prevent sudden cardiac death due to arrhythmias. These devices markedly improve symptoms, quality of life, and survival rates but come with potential complications requiring careful management.

Diagnosis

Diagnosing bacteremia caused by MRSA requires a clinical evaluation, laboratory tests, and imaging studies. This multi-step approach confirms the presence of MRSA in the bloodstream and identifies the infection's source and extent. Critical diagnostic steps include:

A. Blood cultures: Two aerobic, gram-positive blood cultures are obtained from at least two separate venipuncture sites before starting antibiotic therapy, ensuring an aseptic technique to avoid contamination.

***Molecular and advanced diagnostic techniques**:* Polymerase Chain Reaction (PCR) quickly detects MRSA by specific genetic markers, such as the *mecA* gene for methicillin resistance. Matrix-assisted laser Desorption/Ionization-Time of Flight (MALDI-TOF) mass spectrometry rapidly identifies bacteria from cultures based on protein fingerprinting.

Limitation of blood cultures: Although blood cultures are considered the gold standard for diagnosis, conducting additional tests, such as antibiotic susceptibility testing, is crucial for guiding effective treatment. Blood cultures may not always detect MRSA, especially with intermittent bacteremia or low bacterial load. Multiple cultures at different times may be needed, potentially causing delays in diagnosis. Prior antibiotic use can reduce sensitivity, leading to false-negative results.

B. Echocardiography: There are two types of echocardiography: transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE). TTE is the initial non-invasive imaging to detect vegetation on heart valves or other cardiac structures. For accurate diagnosis, TEE is required. It is used to definitively diagnose endocarditis, especially if TTE is inconclusive or if the patient is at high risk for endocarditis.

Diagnosing bacteremia caused by MRSA in patients with cardiac devices presents significant challenges, from the limitation of blood cultures to complexities in imaging and the critical need to differentiate between infection and colonization.

Treatment and challenges

Treating bacteremia caused by MRSA in patients with cardiac devices requires a comprehensive approach, addressing both the infection and the underlying cardiac condition. Key components and challenges of treatment include:

1. Antimicrobial therapy

a) First-line antibiotics: Vancomycin and daptomycin are the primary antibiotics to treat MRSA bacteremia. Vancomycin requires regular monitoring of serum levels to ensure therapeutic efficacy while avoiding toxicity. Daptomycin, an alternative, offers potent bactericidal activity but requires dose adjustments in patients with renal impairment.

b) Combination therapy: Given the difficulty penetrating biofilms, combination antibiotic therapy may enhance efficacy. This approach can more effectively disrupt biofilms and reduce bacterial load than monotherapy. It aims to enhance bacterial eradication, reduced resistance development and improved clinical outcomes. However, a universal treatment algorithm is presently not feasible due to heterogeneity of data.[23] It is further prescribed from present literature to pursue a complete regimen change rather than adding agents to an ineffective regimen.

c) Vancomycin-based regimen: As the main drug of choice for MRSA bacteremia, vancomycin is notably associated with treatment-resistant MRSA. Combination therapies of vancomycin with either B-lactams or ceftaroline has demonstrated increased efficacy in eradicating MRSA.[23] A retrospective cohort study found that Vancomycin combined with B-lactam had microbiological eradication of 96%, compared with 80% of vancomycin alone.[24] However, the increased efficacy has been noted in treating initial MRSA bacteremia versus treatment-resistant MRSA.

d) Daptomycin-based regimen: Daptomycin is typically used as an alternative for vancomycin in the treatment of MRSA. However, studies found that daptomycin used in the setting of vancomycin failure or deep-seated MRSA can result in nonsusceptibility. Daptomycin in combination with B-lactams is noted to be very promising in the setting of vancomycin failure. A case series found that patients who had vancomycin failure were able to achieve blood sterilization within 24-28 hours with daptomycin combined with either nafcillin or oxacillin.[25] Daptomycin in combination with TMP-SMX is also a noted therapy for persistent MRSA bacteremia.[23]

e) Vancomycin or daptomycin with rifampin: Rifampin is added for its ability to penetrate biofilm and enhance intracellular activity. IDSA 2011 guidelines recommend administering intravenous vancomycin plus rifampin 300 mg orally every 8 hours for 6 weeks plus gentamicin 1 milligram/kilogram per dose IV every 8 hours for 2 weeks in patients with MRSA prosthetic valve infective endocarditis. But the use of rifampin needs to be taken carefully viewing the potential of drug interactions.

f) Ceftaroline, 5th generation cephalosporin, has demonstrated activity against MRSA including strains that are resistant to vancomycin and daptomycin. Its use in combination therapy for MRSA bacteremia has been explored to enhance bactericidal activity and prevent the development of resistance. A retrospective study found that the combination therapy with daptomycin and ceftaroline resulted in similar outcomes compared to altered therapy in patients with persistent MRSA bacteremia.[26] And another study found that there was no significant difference in death from all causes at follow up between patients treated with combination therapy of IV vancomycin or daptomycin plus beta-lactam and those treated with standard monotherapy.[27]

g) Dalbavancin: Dalbavancin is a newer therapy for MRSA, particularly acclaimed for its long half-life and outpatient use with weekly or biweekly infusions. A case series study found it was very efficacious in treating persistent MRSA from intravascular sources, specifically from left ventricular assist device, transfemoral aortic valve implantation, and prosthetic aortic valve. The patients were not able to achieve blood sterility with other antibiotic regimens. Treatment with dalbavancin was able to achieve suppression of bacteremia without side effects.[28]

2. Biofilm penetration

Challenge of biofilms: MRSA's ability to form biofilms on cardiac devices significantly complicates treatment. Biofilms are a barrier to antibiotics and immune cells, allowing bacteria to persist despite prolonged antibiotic therapy. Biofilms consist of precise and dense bacterial structures implanted in polysaccharides, conferring resilience and tough shield against antibiotics.

Strategies to overcome biofilms: Innovative strategies are being developed, such as using antibiotics with better biofilm penetration or employing biofilm-disrupting agents. Adjunctive therapies, including using bacteriophages and biofilm-degrading enzymes, are also being explored.[29–31] Taking into consideration crucial genes that MRSA uses for the biofilm formation is offering potential strategies aiming at the elemental and enzymatic properties to fight against MRSA biofilms formation.

3. Device management

Indication for device removal: Persistent bacteremia caused by MRSA, despite appropriate antibiotic therapy, often necessitates the removal of the infected cardiac device. This decision is complex and requires careful consideration of the patient's clinical stability and dependency on the device. European Society of Cardiology 2023 guidelines suggest complete system Removal inpatients with possible cardiac implanted electronic device- related infective endocarditis with occult MRSA and Gram-negative bacteremia in case of persistent bacteremia after a course of antimicrobial therapy.[19]

Timing of re-implantation: If device removal is indicated, re-implantation timing is critical. Ideally, a new device should be implanted only after the infection has been adequately controlled to prevent re-infection. Temporary pacing or support devices may be required in the interim.[31,32]

4. Surgical intervention

Role of surgery: In cases of severe infection, such as endocarditis or abscess formation, surgical debridement or valve replacement may be necessary. Surgical intervention aims to remove infected tissue, drain abscesses, and repair or replace damaged structures.

Risk of surgery: Surgical management of bacteremia caused by MRSA is high-risk, especially in patients with significant comorbidities. Preoperative planning and postoperative care require a multidisciplinary approach to minimize complications.[31,32]

5. Resistance development

Antibiotic stewardship: The emergence of antibiotic-resistant MRSA strains is a significant concern. Judicious use of antibiotics and adherence to antibiotic stewardship principles are essential to limit the development of resistance.

Surveillance and testing: Regular microbiological surveillance and susceptibility testing guide effective treatment adjustments and help detect emerging resistance patterns early.[29,30]

6. Multidisciplinary approach

Collaborative care: The complex bacteremia caused by MRSA in patients with cardiac devices necessitates a collaborative approach. Infectious disease specialists, cardiologists, cardiothoracic surgeons, microbiologists, and pharmacists must work together to optimize treatment plans and patient outcomes.[30,32]

Patient education and follow-up: Educating patients about the importance of adherence to antibiotic regimens and follow-up appointments is crucial for successful outcomes. Regular follow-up ensures early detection of recurrence or complications.

Consideration of the impact of vaccines on the risk of MRSA infection in cardiac patients

Vaccines, along with their adjuvants, plasmids, and components such as endotoxins, can have varying impacts on cardiac health, which may influence the susceptibility to infections like those caused by Methicillin-resistant *Staphylococcus aureus* (MRSA). Influenza vaccination has been associated with a reduced incidence of cardiovascular events, cardiovascular death, and all-cause death in patients with high cardiovascular risk.[33] COVID-19 vaccination is also recommended to reduce COVID-19 complications in patients with chronic coronary disease per public health guidelines.[34] While vaccines are designed to bolster the immune response and protect against infectious diseases, adjuvants are added to enhance this response, sometimes leading to inflammatory reactions that could stress cardiac function, especially in individuals with pre-existing heart conditions.[35] Additionally, the introduction of plasmids and endotoxins during vaccination may trigger immune activation that, in some cases, could disrupt the delicate balance of the immune system,[36] potentially increasing vulnerability to opportunistic infections. This immune modulation can result in transient immunosuppression or dysregulation, which might facilitate MRSA colonization and infection in susceptible populations. As such, understanding these interactions is crucial for evaluating the broader implications of vaccination strategies on cardiac health and the risk of MRSA infections, particularly in patients with implanted cardiac devices who may already be at elevated risk.

Conclusion

Managing MRSA bacteremia in patients with cardiac implantable devices presents significant challenges due to the bacteria's ability to form biofilms on these devices, which makes treatment more difficult. Biofilms create a protective barrier around the bacteria, shielding them from both antibiotics and the immune system, often requiring prolonged, multi-drug therapy. Common treatment options include vancomycin and daptomycin, sometimes in combination with rifampin or newer antibiotics like ceftaroline, to penetrate the biofilm and control the infection. Despite these efforts, however, persistent infections remain common, and the decision to remove the device can be difficult, particularly for patients who rely on it for heart function.

Early and accurate diagnosis is crucial for effectively managing MRSA infections. Blood cultures are typically the primary diagnostic tool, but they can be unreliable, especially if the patient's bacterial load is low or if they've recently received antibiotics. Advanced imaging techniques, such as transesophageal echocardiography (TEE), can provide a clearer picture of how the infection has spread and help guide decisions regarding device management. However, distinguishing between simple colonization and active infection remains a challenge, underscoring the importance of a thorough, multi-faceted diagnostic approach.

In cases of MRSA infections with cardiac devices, the decision to remove the device is often critical. The European Society of Cardiology recommends device removal for persistent MRSA bacteremia, though this decision carries risks and typically requires a collaborative approach involving infectious disease specialists, cardiologists, and surgeons. If removal is necessary, temporary pacing may be used to maintain heart function until the infection is controlled and it is safe to re-implant a new device.

Emerging therapies, such as bacteriophages and biofilm-disrupting agents, offer promising alternatives to conventional antibiotics. Additionally, antibiotic stewardship and ongoing monitoring of resistance patterns are essential for managing MRSA bacteremia effectively, helping to prevent the development of resistance and ensuring continued efficacy of treatments. Given the persistent threat of MRSA in healthcare settings, robust surveillance and targeted therapies are critical to improving patient outcomes and minimizing complications.

In conclusion, the resilience of MRSA and its ability to form biofilms make these infections particularly difficult to treat. Overcoming these challenges will require ongoing advancements in treatment, enhanced collaboration across medical specialties, and patient education to improve outcomes and reduce complications for the most vulnerable individuals.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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